Remarks

The Office Action mailed September 14, 2009 has been received and reviewed. Claims 1, 14, 18, 26, and 33 have been amended, claims 48-51 have been added, and claims 5, 9-13, 32, 36-40 and 44-46 have been canceled, without prejudice. Claims 1-4, 6-8, 14-24, 26-31, 33-35, 41-43, and 48-51 are now pending and under examination. Reconsideration and withdrawal of the rejections are respectfully requested.

Support for amending the independent claims to recite "at least two adaptive mutations" may be found in the specification at, for instance, page, 14, lines 21-23.

Support for amending the independent claims to recite genotype 1a may be found at originally filed claims 5, 25, and 36, and in the specification at, for instance, page 18, lines 23-32, and page 20, line 28 through page 21, line 2.

Support for new claims 48-51 may be found in the specification, for instance, at page 28, lines 3-23.

The Examiner is requested to note that the present application was cited in a provisional double patenting rejection during prosecution of U.S. Patent Application S/N 11/975,658.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 1-8, 14-36, and 41-43 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

In view of this rejection, the claims have been amended to recite "wherein the 5' NTR, the 3' NTR, and the nucleotide sequence encoding the polyprotein are genotype 1a" (independent claims 1, 18, 26, and 33) or "wherein the 5' NTR, the nucleotide sequence encoding the polyprotein, and 3' NTR are genotype 1a" (independent claim 14). In view of this rejection, the independent claims have been amended to recite "at least two adaptive mutations."

The Office states that one of the mutations taught by the specification is K1694R. The

specification does not disclose K1694R; however, it does disclose K1691R, and some claims recite K1691R. Likewise, the Office also states that one of the mutations taught by the specification is Q1609R. The specification does not disclose Q1609R; however, it does disclose Q1067R, and some claims recite Q1067R. For the purposes of replying to this Office Action the Applicant will assume the reference to K1694R and Q1609R were clerical errors and that K1691R and Q1067R were intended by the Office. Please confirm this assumption in the next Communication.

The Office asserts that only two combinations of adaptive mutations are enabled: the combination of S2204I, K1691R, F2080V, and Q1067R, and the combination of S2204I, K1691R, and Q1067R. Office Action at paragraph 12. Applicant respectfully disagrees. The specification provides working examples showing other combinations of adaptive mutations result in replication competent polynucleotides. The combination of S2204I with each of the following: Q1067R, V1655I, K1691R, and K2040R; Q1067R, K1691R, and K2040R; Q1067R, V1655I, and K1691R; Q1067R, K1691R, and F2080V; and Q1067R and K1691R, was shown to result in replication competent polynucleotides (see, for instance, page 46, lines 10-31, page 48, lines 6-22, Figure 4, and Figure 6). Thus, there is no reasonable basis for the Office to assert that only two combinations of adaptive mutations are enabled.

The enablement of the claims is questioned due to the alleged unpredictable effect of random mutations on the replication of an HCV replicon. Office Action at paragraph 15. This assertion of unpredictability is inappropriate here. The mutations recited in the pending claims are not random. The claims recite specific mutations that result in replication of HCV replicons in cultured cell lines. Identifying new adaptive mutations in HCV may include some level of unpredictablity; however, introducing the claimed adaptive mutations into a genotype 1a HCV replicon will predictably not degrade replication of the HCV replicon.

The Examiner notes that the S2204I mutation in combination with Q1067R and F2080V does not result in a replication competent HCV. The Examiner is requested to note that a different set of mutations, S2204I in combination with Q1067R and K1691R, yields a replication

competent HCV. According to the M.P.E.P., the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be operative with expenditure of no more effort than is normally required in the art. M.P.E.P. §2164.08(b). The specification clearly identifies operative embodiments (see, for instance, page 46, lines 10-31, page 48, lines 6-22, Figure 4, and Figure 6). Further, undue experimentation is not required to determine which conceived but unmade embodiments are operable. A considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. M.P.E.P. §2164.06. In view of the working examples and detailed direction and guidance provided by the specification, the skilled person can easily construct HCV that contain the adaptive mutations recited in the claims and then screen them for replication activity.

Applicant respectfully disagrees with the allegation that the claimed combinations of mutations are enabled only when they are present in SEQ ID NO:2. Office Action at paragraph 12. An examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. M.P.E.P. §2164.04. No explanation is provided to support the allegation that only adaptive mutations in SEQ ID NO:2 are enabled.

The Examiner also alleges that the specification fails to describe which 10% of the genome "can be can be modified and how to mutate each of these 10% genetic codes [sic]." Office Action at paragraph 16. A specification does not need to disclose what is well-known to those skilled in the art, and in fact preferably omits that which is well-known to those skilled and already available to the public. M.P.E.P. §2164.01, 2164.05(a). HCV is the most common cause of chronic viral hepatitis in the United States, responsible for the deaths of 8,000 to 10,000 persons annually. Genotype 1a and 1b are the predominant HCV in the United States. This serious public heath issue has resulted in significant amounts of research on HCV, especially genotypes 1a and 1b. The nucleotide sequences of many genotype 1a HCV were known as of the

December 1, 2003, priority date for this patent application, and comparisons of sequence variation between different HCV were available to the public. Moreover, the crystal structures of some HCV proteins were also known at the priority date. Thus, the skilled person would have known which nucleotides and/or amino acids were conserved, and could readily determine which nucleotides could be mutated and not affect replication.

The first paragraph of §112 requires no more than a disclosure sufficient to enable the skilled worker to carry out the invention commensurate with the scope of the claims. It is respectfully submitted that upon reading Applicant's detailed specification the skilled worker would be able to carry out the invention commensurate with the scope of the claims. For at least the reasons provided above, reconsideration and withdrawal of this rejection.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 1-8, 14-35, and 41-43 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserts that the claims fail to specify the reference sequence from where the amino acid positions in the claims are numerated. The traversal of this rejection is respectfully maintained.

The test for definiteness under 35 U.S.C. 112, second paragraph, is whether those skilled in the art would understand what is claimed when the claim is read in light of the specification (M.P.E.P. §2173.02). "In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent" (M.P.E.P. §2173.02). "The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles . . . . Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a

court declare it indefinite" (M.P.E.P. §2173.02).

The specification discloses that the adaptive mutations recited in the claims are relative to the polyprotein after post-translational cleavage of the H77c polyprotein depicted at GenBank accession number AF011751 (see Table 2). The H77c polyprotein depicted at GenBank accession number AF011751 is SEQ ID NO:2. Thus, in light of the specification, the skilled person is able to ascertain where to identify the amino acid positions recited in the claims. Accordingly, the Examiner's request to "specify the reference sequence from where the ordinary number of amino acid residues is counted" is met by the pending claims.

Moreover, the Examiner is requested to consider that HCV is an RNA virus, and it is well known that RNA polymerase replicates RNA at a level of fidelity that is significantly lower than DNA polymerase. Thus there is an expectation that different HCVs will include mutations, and that these mutations will influence the precise location of an adaptive mutation in a polyprotein. Such potential for variation in position is acknowledged in the specification, for example on page 16, lines 5-8, where the numbering system presented in Table 2 indicates that the precise location of the adaptive mutations can vary by 1 to 5 positions between members of the same genotype.

Page 14 line 8 to page 16, line 5 of the specification describes the adaptive mutations of the invention and how they may be located. Each of the claimed mutations is described by reference to its usual position in the polyprotein, and by reference to the amino acids immediately preceding the mutation. For example, the location of an adaptive mutation at amino acid 2204 can be found by locating amino acid 2204. Alternatively, the location of an adaptive mutation at about amino acid 2204 can be found by locating the amino acid sequence SSSA beginning around amino acid 2200 (see page 14, lines 15-20). In this way, the amino acids immediately before the mutation are used as a landmark by the skilled person to determine precisely where the mutation is, regardless of the genotype of the HCV.

For at least these reasons, the claims are not indefinite. Reconsideration and withdrawal of the present rejection is respectfully requested.

Summary

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives at the telephone number listed below if it is believed that prosecution of this application may be assisted thereby.

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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted via the U.S. Patent and Trademark Office electronic filing system in accordance with 37 CFR §1.6(a)(4) to the Patent and Trademark Office addressed to the Commissioner for Patents, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450, on this 14th day of December, 2009.

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